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Formulation-dependent Pharmacokinetics and Pharmacodynamics of Propofol in Rats

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Abstract

Propofol, a highly lipophilic anaesthetic, is commercially formulated as a lipid emulsion (diprivan) for intravenous use. This formulation is characterized by rapid onset and offset of effect after rapid intravenous administration and an effect-site equilibration half-life ($t_{1/2}k_{E0}$) of 1·7 min in rats. Paradoxically these characteristics are usually associated with relatively water-soluble anaesthetics. To test the influence of the formulation on propofol pharmacokinetics, effect-site equilibration kinetics and pharmacodynamics we performed a pharmacokinetic–pharmacodynamic study of propofol in chronically instrumented rats after administration in a lipid-free formulation. In this report we present the results of this study and compare these results with previous data obtained with rats receiving propofol in the emulsion formulation.

Compared with the emulsion formulation the distribution volumes (Vd_C and Vd_{SS}) were significantly higher but the $t_{1/2}k_{E0}$ (2·0 min) was similar for the lipid-free formulation. The concentration–effect relationship was biphasic. Propofol effect-site concentrations required to achieve 50% activation, peak activation, 50% inhibition of peak activation effect and maximum inhibition were significantly lower, indicating a higher apparent steady-state potency for the lipid-free formulation compared with the emulsion formulation. The evanescent characteristics of propofol's effect-time-course disappeared when the anaesthetic was administered in the lipid-free formulation.

These results suggest that the nature of the formulation can profoundly influence the clinical characteristics of intravenously administered drugs by modifying the pharmacokinetics or pharmacodynamics or both.

The rationale for formulating intravenous drugs as emulsions or with co-solvents is usually driven by the biopharmaceutical concern of limited aqueous solubility (Von Dardel et al 1976; Hogskilde et al 1987; Clarke 1992; Powell et al 1992). Lipid-soluble drugs are frequently solubilized in cremophor EL or organic solvents (propylene glycol). However, use of cremophor and propylene glycol as solvents has been associated with hypersensitivity reactions (Dye & Watkins 1980; Huttel et al 1980) and venous irritation (phlebitis, thrombosis and thrombophlebitis (Kawar & Dundee 1982)). Intravenous administration of anaesthetic agents as simple solutions has caused pain, thrombophlebitis and irritation on injection (Kawar & Dundee 1982; Clarke 1992). Pain on injection has been related to high free-concentrations of the drug (Klement & Arndt 1991). Incorporation of lipid-soluble drugs in lipid emulsion has been shown to reduce adverse events associated with the non-aqueous solvents (Von Dardel et al 1976; Glen & Hunter 1984; Clarke 1992; Westrin 1992; Westrin et al 1992).

In addition to enhancing solubility, intravenous emulsion formulations can have an impact on the pharmacokinetics of drugs. Lipid emulsions have been shown to modify the disposition of cyclosporin (Shah & Sawchuk 1991), D-α-tocopherol (Hidiroglou 1991) and other compounds. Although the time-course of a drug in blood (pharmacokinetics) can be altered by emulsion formulation, the impact of intravenous lipid emulsions on the pharmacodynamics (concentration–effect relationship) has not been systematically and rigorously investigated.

Propofol (2,6-diisopropylphenol) is a highly lipophilic (log octanol–water partition coefficient

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4·33 (Chou & Jurs 1980)) anaesthetic agent that is commercially formulated in a lipid emulsion (diprivan; Zeneca Pharmaceuticals) for intravenous use. The administration of propofol formulated in emulsion by rapid intravenous injection produces a rapid onset of effect, a brief but profound level of anaesthesia and a short duration of sleep. Such effect-time profiles are usually associated with relatively water-soluble anaesthetics. A recent report from our laboratory compared the time-course of the effect of propofol in rats on the basis of electroencephalographic (EEG) measurements after administration of propofol in either emulsion or lipid-free formulations (Dutta & Ebling 1997b). At equivalent doses a delayed onset, a lower maximum intensity of effect and a prolonged sedative effect were observed for the lipid-free formulation. This sluggish effect-time profile is more in accord with the high lipophilicity of propofol. Thus it appears that intravenous formulation profoundly influences the clinical characteristics of propofol.

The basis of the time-course of the intensity of the pharmacological effect of any drug arises from three fundamental properties: the time-course of drug concentration in the plasma (pharmacokinetics), the plasma-effect-site equilibration kinetics (conduction; (Holford & Sheiner 1981; Veng-Pedersen & Gillespie 1988)), and the relationship between effect-site drug concentration and the intensity of the pharmacological effect (pharmacodynamics). These three essential properties must first be separated and then characterized to enable better appreciation of the mechanism creating the observed change in effect-time profiles and clinical behaviour. To accomplish this a combined pharmacokinetic–pharmacodynamic study was performed on chronically instrumented rats that received propofol formulated in a lipid-free vehicle. In this report we present the results of this study and compare them with previous data obtained with rats receiving propofol in emulsion formulation (Dutta et al 1997).

Materials and Methods

Lipid-free formulation

We have previously reported the preparation of this lipid-free formulation of propofol (Dutta & Ebling 1997b). A brief description is provided here. Because of the limited solubility of propofol, its administration in a lipid-free vehicle required the development of a unique administration system using two syringe pumps (Harvard model 22). This lipid-free formulation is prepared in-situ during the infusion process. Propofol oil (97% pure; Aldrich) was diluted (approximately 1 : 5) with ethanol and placed in a 250-μL gas-tight syringe on the first pump. A carrier solution similar in composition to the diluted aqueous phase of the commercial emulsion preparation (1 part 22·5 mg mL^{-1} glycerol in water–3 parts 5% dextrose USP), was placed in a 5-mL gas-tight syringe on the second pump. The two solutions, propofol in ethanol and the carrier solution, were simultaneously infused into a pre-primed 22G mixing tee tube. The outflow from the mixing tee tube was connected to the rat's jugular cannula by means of a short piece of PE50 tubing. The flow rates of the component solutions were 30–60 μL min^{-1} kg^{-1} for the propofol in ethanol solution (pump 1) and 2·5 mL min^{-1} kg^{-1} for the carrier solution (pump 2). The flow rate of pump 1 was adjusted to achieve propofol infusion rates of 6·25 or 12·5 mg min^{-1} kg^{-1}.

Animal instrumentation and experimental design

Male Wistar rats, 445 ± 24 g, chronically instrumented with EEG electrodes and intravenous and intra-arterial catheters were used to quantify the extent of central nervous system depression resulting from administration of propofol in lipid-free vehicle. A detailed description of animal instrumentation and experimental methods can be found in our previous reports (Dutta & Ebling 1997b; Dutta et al 1997).

The doses used in this study were based on our previous experience with the emulsion formulation. Propofol administered to rats as an emulsion at a rate of 6·25 mg min^{-1} kg^{-1} produces isoelectric EEG activity (EEG burst suppression) within 2 min of the start of the infusion (Dutta et al 1997). In this study propofol was infused in lipid-free formulation at rates of 6·25 (n = 7) or 12·5 (n = 7) mg min^{-1} kg^{-1} for 2 min. The low dose failed to produce EEG burst suppression whereas the high dose produced transient EEG burst suppression similar to that achieved by the emulsion formulation administered at half the rate.

Ethanol present in the lipid-free formulation was infused at a rate of 50 μL min^{-1} kg^{-1}. Assuming a blood volume and total body water of 5 and 70% body weight, respectively, this dose (100 μL kg^{-1}) of ethanol would theoretically produce peak ethanol blood concentrations in the range 0·01–0·2%. We have previously shown (Dutta & Ebling 1997b) that this dose of ethanol has no effect on animal behaviour or processed EEG effect.

Multiple 400-μL arterial blood samples were drawn at a rapid rate during and shortly after termination of the infusion for the determination of propofol plasma concentrations. During the terminal disposition phase, samples were taken less

frequently. To prevent hypovolaemia the sampled volume was immediately replaced with 800 μL saline; haematocrit never fell below 35% during the study. To measure propofol drug effect a four-lead EEG was recorded during the study on a model 79 EEG physiograph (Grass Instruments, Quincy, MA) with 100 Hz high pass, 0·3 Hz low pass, and 60 Hz notch filter with a gain of 15 μV mm^{-1}. Animals were not restrained during the study. Heart rate was monitored during the study and ventilatory support was provided as required if heart rate fell below 250 beats min^{-1} (Dutta & Ebling 1997b).

HPLC-EC analysis of propofol

Propofol concentrations in plasma and diluted dosing solutions were determined by use of a previously reported (Dowrie et al 1996; Dutta et al 1997) specific and unbiased reversed phase HPLC-EC method. Intra- and inter-day variability were below 15% in the 0·1–10 μg mL^{-1} concentration range.

EEG recording and processing

Propofol can cause profound changes in EEG activity and this has been used as a surrogate measure of anaesthetic effect. Propofol drug effect was assessed from the EEG signal processed by aperiodic analysis using the total number of EEG waves s^{-1} from 0·5 to 30 Hz. A total of 200 time-EEG effect data pairs were collected for each rat. The details of EEG recording and processing have been reported elsewhere (Ebling et al 1991; Dutta et al 1997).

Pharmacokinetic–pharmacodynamic analysis

Pharmacokinetic analysis was performed as previously reported (Dutta et al 1997). A two- or three-compartment model was fitted to the arterial plasma concentration–time profile using Adapt II (D'Argenio & Schumitzky 1979). The estimated intercepts and slopes were used for calculation of an array of pharmacokinetic parameters. Initially pharmacodynamics was examined for each animal by plotting the arterial plasma concentration against the EEG effect. These plots showed profound hysteresis. This hysteresis was collapsed using a semi-parametric technique (Verotta & Sheiner 1987) to reveal the apparent effect-site concentration-effect relationship and for estimation of $t_{1/2}k_{E0}$. A parametric pharmacodynamic model was proposed to characterize the biphasic nature of the effect-site concentration-effect relationship. Subsequently a combined pharmacokinetic–pharmacodynamic model was used to fit the EEG effect-time data and descriptors were used to summarize the biphasic concentration-effect relationship as reported previously (Dutta & Ebling 1997a; Dutta et al 1997).

Statistics

Mean values of pharmacokinetic parameters and pharmacodynamic descriptors were tested for significant difference from those previously reported (Dutta et al 1997) for the emulsion formulation by use of a two-tailed t-test ($P < 0.05$).

Results

Figure 1 shows the arterial plasma concentration–time profiles of propofol in 20 rats during and after administration of propofol in lipid-free formulation or emulsion (Dutta et al 1997)). Propofol arterial plasma concentration–time profiles for the emulsion formulation had a peak value of 10–20 μg mL^{-1} followed by a 10-fold decline in concentration within 15–20 min. This rapid distribution was followed by a highly variable terminal disposition phase. An initial 10-fold decline in pro-

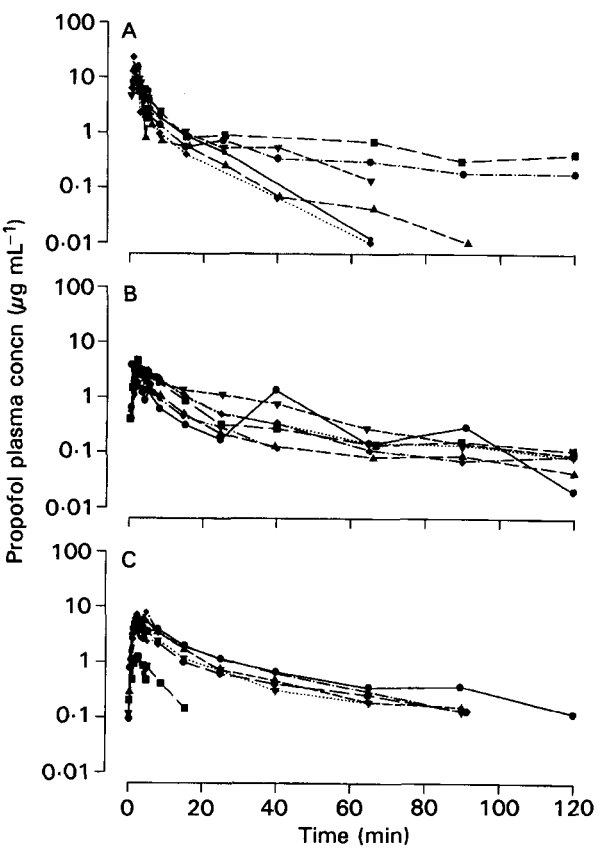

Figure 1. Plasma concentration–time profiles for 20 rats receiving an infusion of propofol in emulsion formulation (A: diprivan; n = 6) at 6.25 mg min^{-1} min^{-1} kg^{-1} or lipid-free formulation at 6·25 mg min^{-1} kg^{-1} (B: n = 7) or 12·5 mg min^{-1} kg^{-1} (C: n = 7) for 2 min. Symbols represent measured concentrations of propofol in plasma.

pofol arterial plasma concentrations occurs over 30–40 min for the lipid-free formulation at both dose levels indicating much slower distribution kinetics. This phase was followed by a less variable terminal disposition. The peak plasma concentrations at the low (Figure 1B) and high (Figure 1C) doses were approximately 2–4 $\mu g\,mL^{-1}$ and 5–8 $\mu g\,mL^{-1}$, respectively.

Table 1 compares the pharmacokinetic parameters of propofol after administration in the two formulations. No statistically significant differences could be detected between the calculated pharmacokinetic parameters for the two doses of propofol in the lipid-free formulation. The pooled parameter values from all rats are presented. The pharmacokinetic character of propofol was altered after administration as the lipid-free formulation. The volume of distribution at steady-state (Vd_{SS}) and the volume of the central compartment (Vd_C) increased by 3- and 10-fold, respectively. Mean transit time through the central compartment was extended 9-fold. Although not statistically significant, elimination clearance (CL) tended to be larger. CL was greater than hepatic blood flow (Ebling et al 1994) for both formulations. The mean residence time and terminal half-life were not affected by the formulation.

Collapsing the hysteresis loop between arterial concentration and EEG effect reveals the relationship between the apparent effect-site concentration and EEG effect. Figure 2 presents this relationship for lipid-free and emulsion (Dutta et al 1997) formulations. With the exception of one animal the concentration–effect relationship for the lipid-free formulation was shifted to the left compared with the emulsion formulation. The inter-animal variability in the concentration–effect relationships was, in general, much lower than that observed for pharmacokinetics for the two formulations.

Table 1. Pharmacokinetic parameters of propofol in rats†.

Formulation	Lipid free	Emulsion‡
Weight (g)	445 (6)	515 (16)
Volume of the central compartment ($L\,kg^{-1}$)	4·1 (41)*	0·33 (70)
Distribution clearance ($L\,min^{-1}\,kg^{-1}$)	0·20 (38)	0·22 (45)
Elimination clearance ($L\,min^{-1}\,kg^{-1}$)	0·34 (51)	0·16 (27)
Volume of distribution at steady state ($L\,kg^{-1}$)	9·7 (59)*	3·2 (76)
Mean transit time in the central compartment (min)	9·2 (45)*	1·0 (82)
Mean residence time of the drug in the body (min)	29 (70)	25 (100)
Terminal half-life (min)	23 (85)	27 (86)

†Mean values of results from 14 rats; the numbers in parentheses are the coefficients of variation (%). ‡Previously reported data (Dutta et al 1997); n = 6. *$P < 0.05$, significantly different from result for emulsion.

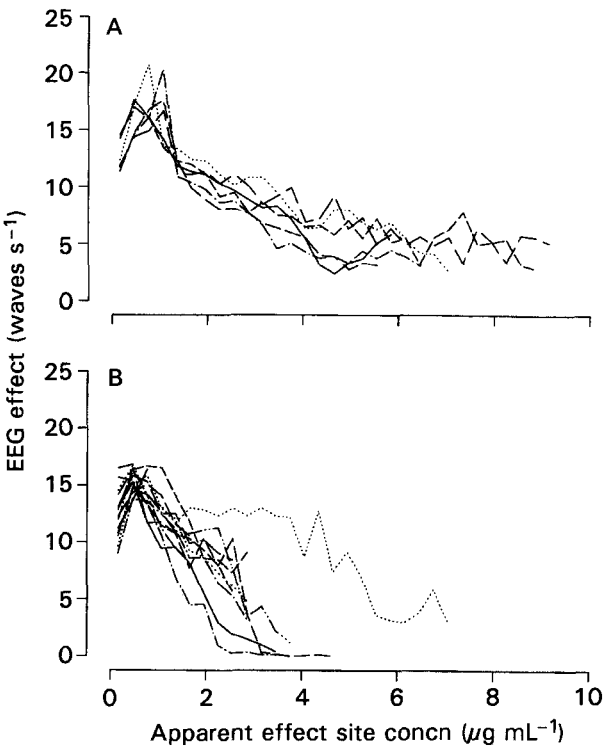

Figure 2. Biphasic relationships between EEG effect and apparent effect-site concentration for 20 rats. A. The concentration-effect relationships for rats receiving propofol in an emulsion (diprivan; n = 6). B. The relationships for rats receiving the lipid-free formulation (n = 14).

Pharmacodynamic descriptors for the biphasic concentration–effect relationship of propofol in the two formulations are compared in Table 2. The peak EEG effect was lower for the lipid-free formulation. The apparent effect-site (or apparent steady-state) concentrations required to achieve 50% activation, peak activation, 50% inhibition of peak activation effect and maximum inhibition were significantly lower for the lipid-free formulation indicating a higher apparent steady-state potency for this formulation compared with the emulsion. Also reported in this table is the effect-site equilibration half-life ($t½k_{E0}$). No statistically significant difference was detected between effect-site turnover values ($t½k_{E0}$) for the two formulations.

Discussion

Elimination clearance was higher than liver blood-flow (Ebling et al 1994) for both formulations; this is consistent with observations of extra-hepatic

Table 2. EEG effect descriptors of pharmacodynamics of propofol†.

Formulation	EEG activity (waves s^{-1})		Estimated effect site concentration at different effect intensities ($\mu g\ mL^{-1}$)					Equilibration half-life (min)
	Baseline	Peak	50% activation‡	Peak activation	Baseline§	50% inhibition§,††	Maximum inhibition§	
Lipid free	10 (7)	16 (6)*	0·19 (57)*	0·38 (57)*	1·6 (21)	2·0 (23)*	3·5 (11)*	2·0 (48)
Emulsion‡‡	11 (6)	18 (4)	0·36 (76)	0·64 (35)	1·9 (18)	2·8 (19)	7·2 (22)	1·7 (32)

†Mean values of results from 14 rats are reported; numbers in parentheses indicate coefficient of variation (%); ‡Effect site concentration at effect intensity of (Baseline + Peak activation)/2 before peak activation effect. §Post-peak activation effect. ††Effect site concentration at 50% inhibition of peak activation effect (post-peak activation). ‡‡Previously reported data (Dutta et al 1997); n = 6. *$P < 0·05$, significantly different from result for emulsion.

metabolism in man (Kanto & Gepts 1989). Because propofol distribution (CL_D) and elimination (CL) is believed to be perfusion-limited, a major formulation-induced increase in clearance processes was unexpected. The increase in elimination clearance after administration of the lipid-free formulation exceeds liver blood-flow. Thus the trend toward higher elimination clearance observed with the lipid-free formulation suggests the possibility of an increase in extra-hepatic metabolism resulting from enhanced delivery of propofol to extra-hepatic elimination sites in the body.

The nature of the formulation primarily influenced the distribution volumes. Administration of propofol in a lipid-free vehicle resulted in a 10-fold increase in Vd_C. Not only is Vd_C increased for the lipid-free formulation it also encompasses a greater extent of propofol's total distribution space (40% compared with 10% for the emulsion). Because the pharmacokinetic parameters are based on arterial concentrations, a possible mechanism for an expanded Vd_C is enhanced first-pass pulmonary uptake and slower pulmonary transit after intravenous administration in the lipid-free formulation. Enhanced first-pass pulmonary uptake would reduce peak arterial plasma concentrations; this is consistent with the behaviour observed in this study. First-pass pulmonary uptake has been shown to reduce significantly peak plasma concentrations of lipid-soluble drugs such as fentanyl (Roerig et al 1987, 1989; Taeger et al 1988). The greatly increased central volume (Vd_C) with only moderate changes in clearance accounts for the extended mean transit time through the central compartment.

Additionally a 3-fold increase in Vd_{SS} for the lipid-free formulation indicates that the emulsion might prevent uptake of propofol to kinetically significant tissues. Higher Vd_{SS} and CL observed for the lipid-free formulation can account for the lack of differences between the mean residence times and the terminal half-lives for the two formulations. Similar effect-site equilibration half-lives for the two formulations suggest that the rate at which the propofol concentration at the hypothetical effect-site equilibrates with propofol plasma concentration is not influenced by formulation.

As illustrated in Figure 2, the apparent steady-state potency of propofol administered in the lipid-free formulation was higher than that for the emulsion formulation. The steady-state potency characterized by the steady-state arterial plasma concentration–effect relationship (pharmacodynamics) is independent of the pharmacokinetics and other distribution effects (e.g. effect-site turnover). The higher potency of the lipid-free formulation indicates that for a given steady-state plasma concentration, a more intense effect is elicited by this formulation than by the emulsion. Formulation-induced changes in brain-plasma solubility could potentially explain the higher steady-state potency observed for the lipid-free formulation. Enhanced brain solubility after administration in lipid-free formulation is consistent with an overall increase in tissue-to-plasma partitioning (larger Vd_{SS}).

Dose potency, on the other hand, is the dose required to achieve a pre-defined effect end-point after transient drug administration. It depends both on the pharmacokinetics and on the concentration-effect relationship of the drug. On the basis of the time-course of the EEG effect we have previously demonstrated (Dutta & Ebling 1997b) that propofol has a higher dose potency when administered in the emulsion formulation compared with administration in the lipid-free formulation. The results of this pharmacokinetic-pharmacodynamic study in comparison with that previously reported (Dutta et al 1997) re-confirms the higher dose potency of propofol when administered in emulsion. The reduced dose potency of the lipid-free formulation can be explained by the increased distribution volumes. The large Vd_C for the lipid-free formulation attenuates the rise in arterial plasma concentrations during infusion. A larger dose of propofol must be

infused to fill this volume if comparable peak arterial plasma (and brain) concentrations are to be achieved. Infusing the lipid-free formulation at $12{\cdot}5\,mg\,min^{-1}\,kg^{-1}$ produced peak plasma concentrations that were half those obtained after $6{\cdot}25\,mg\,min^{-1}\,kg^{-1}$ infusion with the emulsion formulation. Although the doses and peak plasma concentrations differed they were equally effective because propofol administered in the lipid-free formulation has twice the steady-state potency of the emulsion formulation.

In conclusion, in the absence of emulsion the volume of distributions increase, resulting in lower plasma concentrations. The decrease in apparent solubility of propofol within the circulation with the lipid-free formulation alters plasma-effect-site partitioning which increases the apparent steady-state potency. However, formulation had no influence on effect-site kinetics ($t½\,k_{E0}$). These phenomena interact to reduce the dose potency of propofol in the lipid-free formulation and impart sluggish effect-time profiles.

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